Adynamic bone disease

Presented by

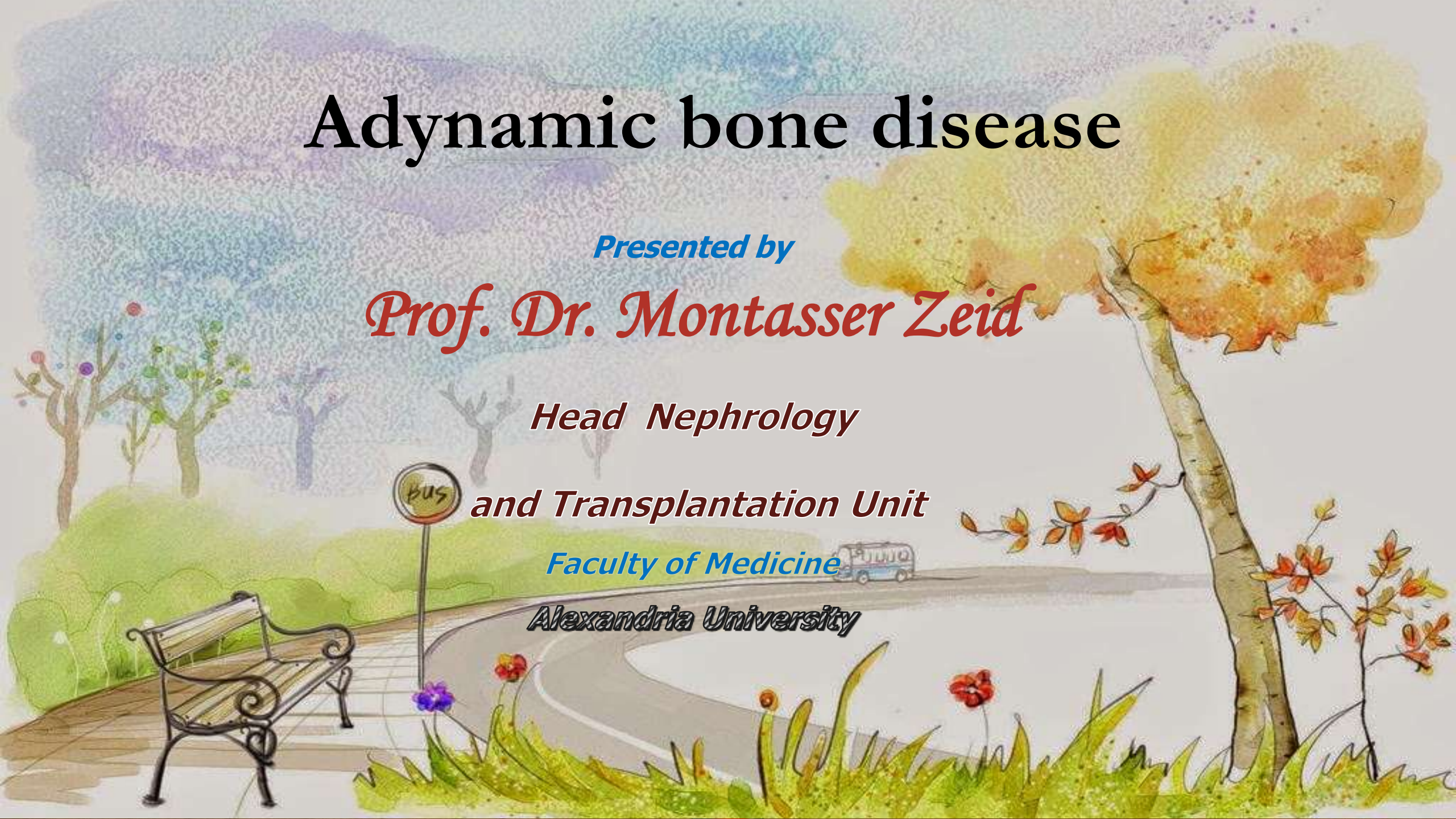
Prof. Dr. Montasser Zeid

Head Nephrology

and Transplantation Unit

Faculty of Medicine

Alexandria University



Renal osteodystrophy

- Renal osteodystrophy is currently defined as an alteration of bone morphology in patients with chronic kidney disease (CKD).
- It is one measure of the skeletal component of the systemic disorder of chronic kidney disease-mineral and bone disorder (CKD-MBD).
- The term "renal osteodystrophy" was coined in 1943, 60 years after an association was identified between bone disease and renal failure.

Renal osteodystrophy cont….

The traditional types of renal osteodystrophy have been defined on the basis of turnover and mineralization as follows:

- **mild, slight increase in turnover and normal mineralization;**
- **osteitis fibrosa, increased turnover and normal mineralization;**
- **osteomalacia, decreased turnover and abnormal mineralization;**
- **adynamic, decrease turnover and acellularity;**
- **mixed, increased turnover with abnormal mineralization.**

Renal osteodystrophy cont.…

- **A Kidney Disease: Improving Global Outcomes report has suggested that bone biopsies in patients with CKD should be characterized by determining bone turnover, mineralization, and volume (TMV system).**

Definition

- **CKD-MBD is defined as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:**

1) abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism;

2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength (renal osteodystrophy); and

3) vascular or other soft-tissue calcification.

Signs and symptoms

Renal osteodystrophy may exhibit no symptoms; if it does show symptoms, they include:

- **Bone pain**
- **Joint pain**
- **Bone deformation**
- **Proximal muscle weakness**

Signs and symptoms cont……

- **Bone fracture (ribs , vertebral bodies , pelvis and hips)**
- **The broader concept of chronic kidney disease-mineral and bone disorder (CKD-MBD) is not only associated with fractures but also with cardiovascular calcification, poor quality of life and increased morbidity and mortality in CKD patients (the so-called bone-vascular axis).**

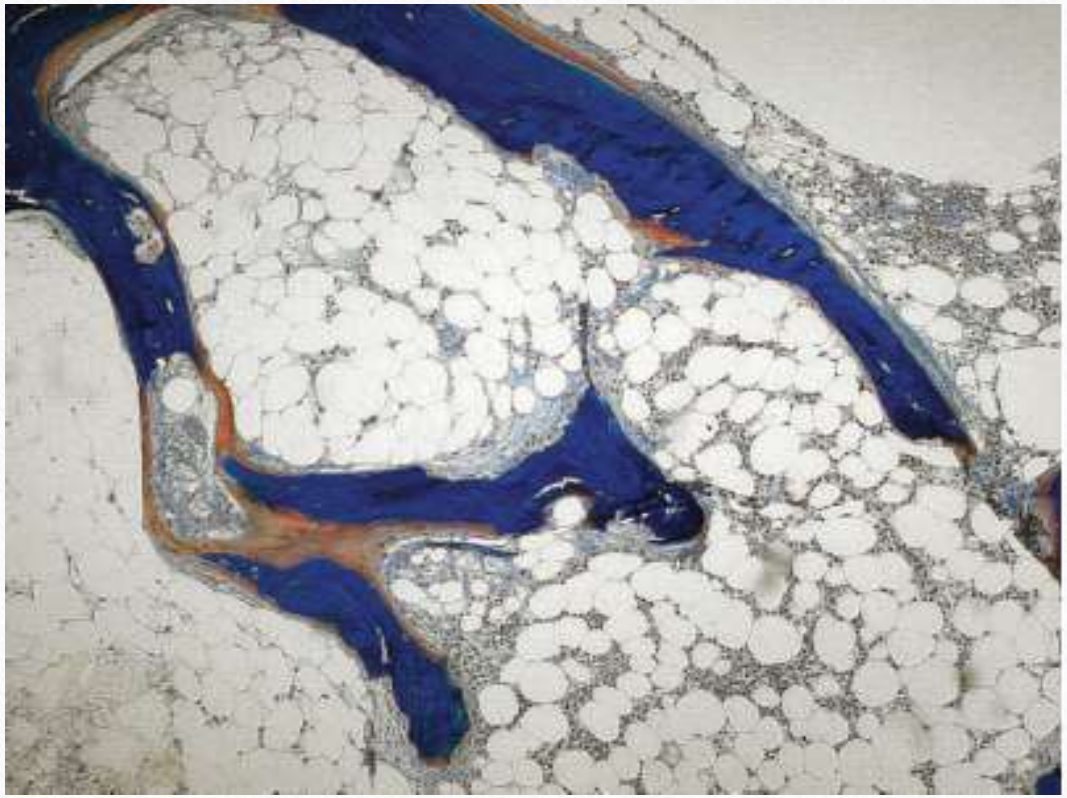
What is ABD?

- The term ‘aplastic’ or ‘adynamic’ bone disease was introduced in the early 1980s .
- ABD is characterized by a low-bone turnover without osteoid accumulation, i.e. with a thin osteoid seam.
- Both the rate of collagen synthesis by osteoblasts and the subsequent mineralization of bone collagen are subnormal.

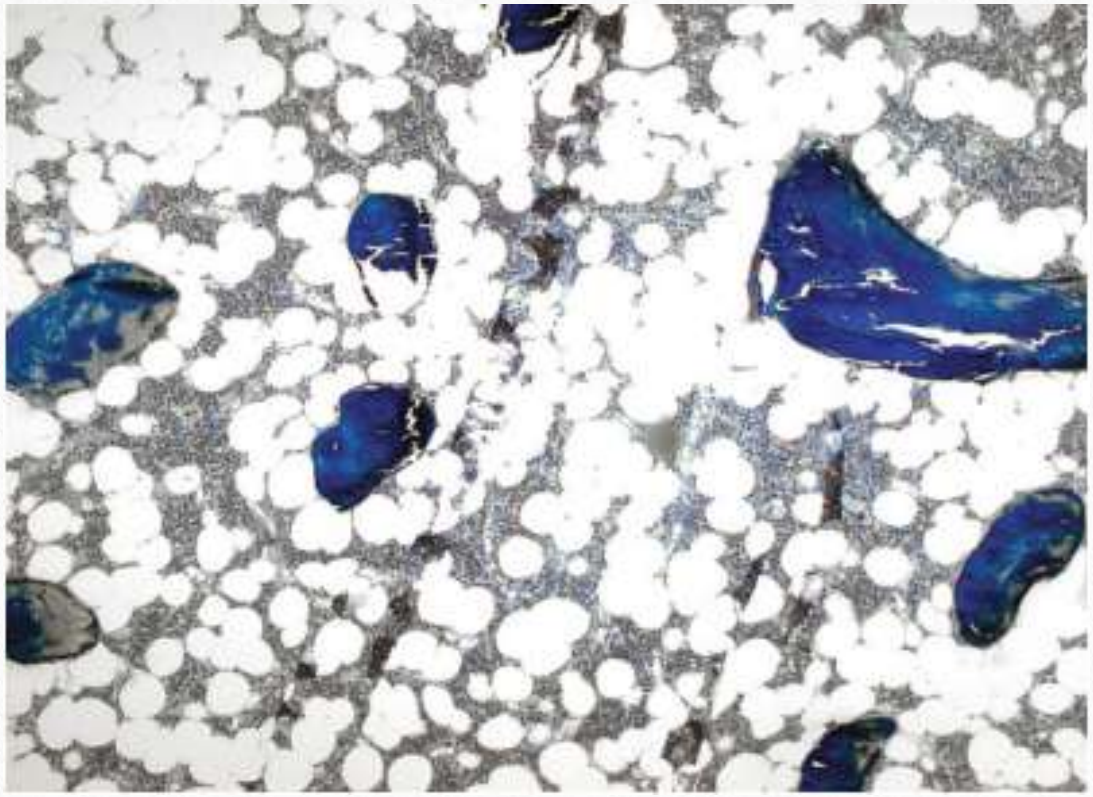
What is ABD? Cont..

- The latter distinguishes ABD from the second low-turnover form, i.e. osteomalacia, where a mineralization defect exceeds the defects in bone formation, resulting in a relative osteoid excess .
- In ABD, there are few or no osteoblasts, and minimal or no peritrabecular fibrosis or marrow fibrosis (in contrast to osteitis fibrosa).

ABD in bone histomorphometry



Mixed uraemic osteodystrophy: high resorptive activity, osteoid accumulation, peritrabecular fibrosis (Goldner stain) (courtesy of Dr. G. Lehmann, Jena).



Adynamic renal osteodystrophy: absence of cellular activity and osteoid, low cancellous bone volume (osteopenia) (Goldner stain) (courtesy of Dr. G. Lehmann, Jena).

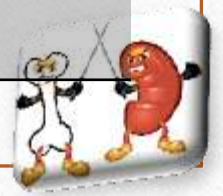
How to diagnose the subtype of renal osteodystrophy

- The gold standard for the diagnosis and classification of ROD is histomorphometric analysis of an undecalcified bone sample .Pre-biopsy in vivo tetracycline labelling as well as amyloid and aluminium stains are required for complete diagnostic work-up.
- A combination of dynamic and static bone parameters, both of cortical and trabecular bone, gives a complete overview upon bone metabolism.

KDIGO and NKF-KDOQI guidelines recommend a bone biopsy in the following cases

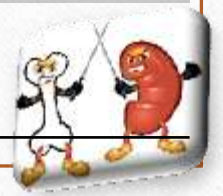
- **Table: Possible indications for an iliac crest bone biopsy in renal osteodystrophy**

If a CKD patient with serum levels of intact PTH (iPTH) between 100 and 500 pg/mL (11.0–55.0 pmol/L) develops unexplained hypercalcaemia, bone pain or an increase in bone alkaline phosphatase activity
Inconsistencies among biochemical parameters that do not allow a definitive interpretation of bone metabolism
Unexplained skeletal fracture or bone pain
In the absence of other known causes of a bone fracture (e.g. malignancy); in the case of low trauma, unexplained fracture



- **Table: Possible indications for an iliac crest bone biopsy in renal osteodystrophy cont..**

Severe progressive vascular calcification
Unexplained hypercalcaemia
Suspicion of aluminium overload or toxicity (or possibly other metals like strontium), especially before chelation treatment due to possible side effects of DFO
Before parathyroidectomy if there has been significant exposure to aluminium in the past or if the results of biochemical determinations are not consistent with advanced secondary or tertiary hyperparathyroidism
Consider a biopsy before beginning treatment with bisphosphonates



Assessment of renal osteodystrophy without a bone biopsy

Assessment of renal osteodystrophy without a bone biopsy

- Whereas plasma iPTH levels at the extremes, i.e. 800 pg/ml, are usually associated with ABD and high-turnover bone disease, respectively, in particular levels between about 100 and 500 pg/ml exhibit variable associations with types of bone lesions.

- This diagnostic uncertainty of intermediate, K/DOQI target-compliant PTH levels has recently been confirmed by bone biopsy studies from Brazil and Portugal .

Assessment of renal osteodystrophy without a bone biopsy

Cont……

- The situation is complicated further by wide variations in iPTH results if different test assays are employed and by potentially variable ratios of agonistic (PTH1–84) and antagonistic (PTH7–84) PTH forms.
- Bone alkaline phosphatase (BAP) is probably the single most useful biochemical parameter for the assessment of bone formation.

Assessment of renal osteodystrophy without a bone biopsy

- Elevated levels of bone alkaline phosphatase virtually exclude an adynamic renal bone disease; however, elevations of **BAP** along with total AP may be seen in cases of severe osteomalacia. Combinations of biochemical markers hold promise ,at least for the differentiation for high-turnover versus adynamic forms.
- Such combinations could be, for example, **iPTH** plus **osteoprotegerin** or **iPTH** plus **bone-specific alkaline phosphatase** .
- Another approach is to measure the ratio of **PTH(1–84)** to **PTH(7–84)**

When does ABD occur in the course of CKD?

- ABD frequently occurs before ESRD is reached.
- Bone biopsies in patients new on dialysis or with advanced CKD (mean age 54 ± 12 years) revealed ABD in 23% of the patients .None of these patients had received calcitriol or aluminium during the course of CKD.
- An even higher ABD prevalence of 49% in predialysis CKD stage 5 patients was reported
- The prevalence of ABD was 13% in patients with a creatinine clearance of 20 ± 12 ml/ min .No data are available on the evolution of ABD in patients who progress from CKD stages 3 to 5.

What are risk factors for the development of ABD?

- **Table : Factors associated with a high prevalence of ABD**

  - **High calcium load**
  - **Low PTH levels**
  - **Vitamin D over-treatment**
  - **Increasing age of the dialysis patients**
  - **High prevalence of diabetes mellitus**
  - **CAPD compared to haemodialysis**

ABD and calcium metabolism

- **ABD** is characterized by a reduced ability to incorporate serum calcium into the bone compartment.
- In agreement with this, low biochemical markers of bone turnover predicted the development of hypercalcaemia after the initiation of calcium carbonate. The reduced bone capacity to buffer calcium loads in **ABD** has now been widely confirmed

ABD and ectopic calcification

- Cardiovascular calcifications and associated mortality are prominent clinical problems in patients with ESRD. Several studies noted a relation between bone metabolism and such calcifications;
- In 224 prevalent Turkish haemodialysis patients, low turnover was detected in 75% of the bone biopsies .Patients with the lowest bone activation frequencies, i.e. the lowest bone turnover, exhibited the most pronounced coronary artery calcification (CAC) scores.

ABD and ectopic calcification cont..

- Calcific uraemic arteriolopathy (CUA), formerly called calciphylaxis, has also been linked to ABD : five out of seven patients with CUA had biopsy-confirmed ABD.

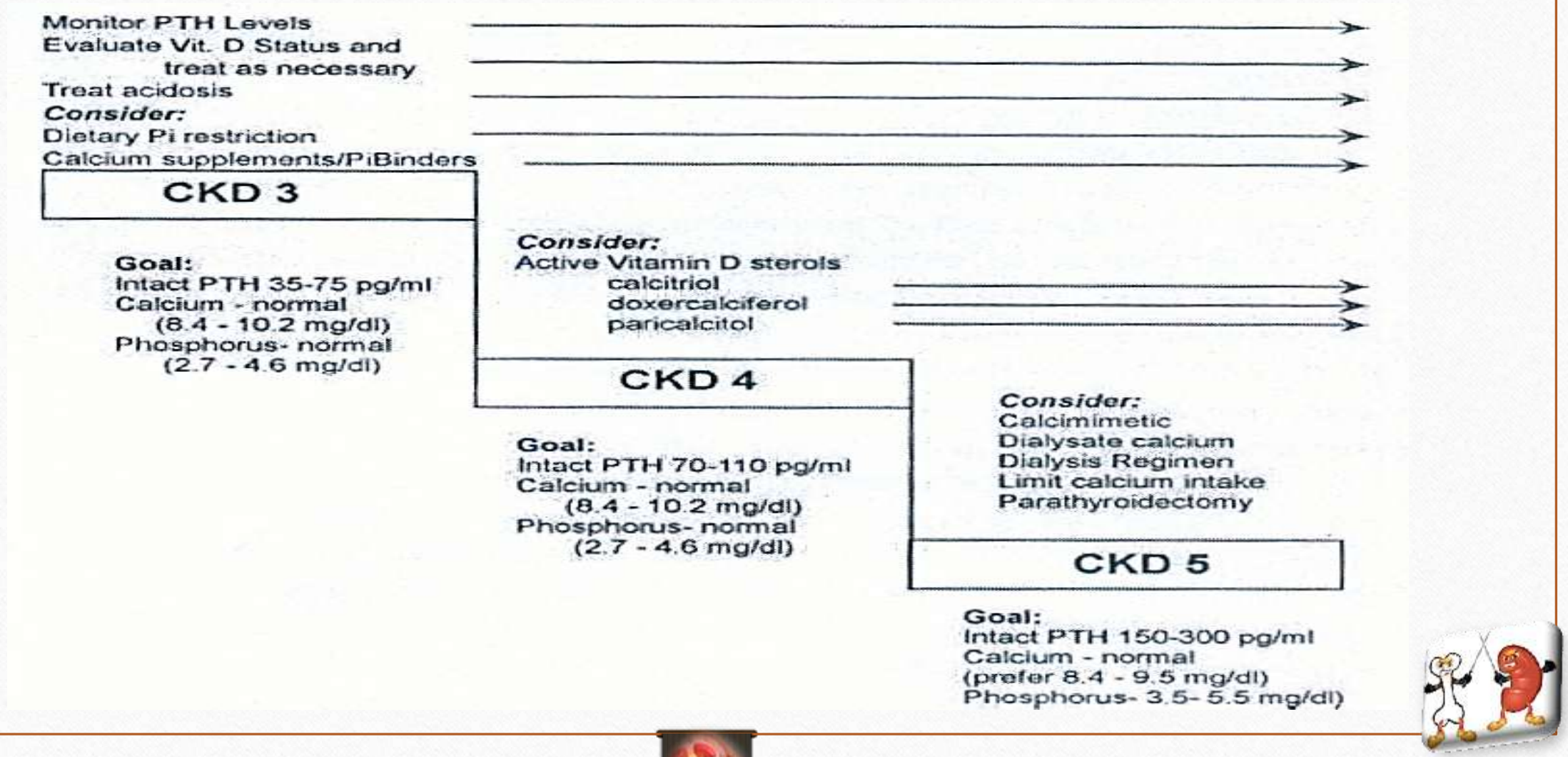
Prevention and Management of Metabolic Bone Disease in CKD

- **The objectives for the management of metabolic bone disease in patients with CKD are to maintain the blood levels of calcium and phosphorus as close to normal as possible and to undertake measures to prevent the development or to begin the treatment of established hyperparathyroidism and to prevent the development of parathyroid hyperplasia.**

Prevention and Management of Metabolic Bone Disease in CKD

- An additional goal is to prevent extraskeletal calcifications and to avoid, over- suppression of bone turnover to the extent that adynamic bone might be induced.
- It also is necessary to avoid the accumulation of substances that may be toxic to bone, such as aluminum.

Figure "stepped-care" approach to the prevention and treatment of secondary hyperparathyroidism in CKD.



NKF KDOQI GUIDELINES

GUIDELINE 13C. ADYNAMIC BONE DISEASE

- **13c.1** Adynamic bone disease in stage **5 CKD** (as determined either by bone biopsy or intact **PTH <100 pg/ml** [**11.0 pmol/L**]) should be treated by allowing plasma levels of intact PTH to rise in order to increase bone turnover. (OPINION)
- **13C.1a** This can be accomplished by decreasing doses of calcium-based
- phosphate binders and **vitamin D** or eliminating such therapy. (OPINION)

Management of the patient with ABD

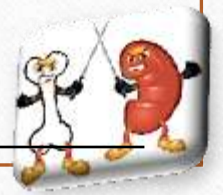
Table : Therapeutic strategies in ABD

- Stop calcium-containing phosphate binders and replace with non-calcium-, non-aluminium-containing phosphate binders
- Assess oral dietary calcium intake and reduce to < 2000 mg/day
- Reduce or stop active vitamin D compounds
- Lower dialysate calcium to 1.25 mmol/L or below
- In selected cases consider a biopsy to confirm diagnosis and to assess bone aluminium content and distribution

Management of the patient with ABD

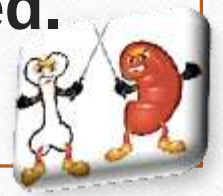
Table : Therapeutic strategies in ABD cont..

- Stop aluminium exposition; consider aluminium mobilization and removal (DFO treatment)
- Consider PTH(1–34) in ABD plus severe fracturing osteoporosis
- Calcimimetics and calcilytics currently of unknown value
- Avoid bisphosphonates, strontium and fluoride administration



Teriparatide as a bone-stimulating agent

- The daily subcutaneous application of **PTH**, teriparatide, is a powerful anti-osteoporotic treatment.
- In theory, teriparatide offers the chance to restore bone metabolism in patients with **ABD**.
- teriparatide (e.g. 20 µg s.c. three times per week after haemodialysis) has been used in bone biopsy-confirmed **ABD** patients with severe fracturing osteoporosis. Reductions of bone pain and transient increases of bone-specific alkaline phosphatase have been reported.



Restoring the pulsatile PTH secretion pattern

- The biological action of PTH on bone largely depends on pulsatile PTH secretion .
- This may explain the risk for ABD in patients receiving active vitamin D or peritoneal dialysis, since in the former case vitamin D activity builds up over days and then continuously suppresses PTH release, whereas in PD patients there is often a constant exposure to high calcium dialysate levels, in contrast to the fluctuating calcium level in HD patients.

Restoring the pulsatile PTH secretion pattern cont.…

- **Two classes of compounds may help re-establish a pulsatile, oscillatory secretion pattern of PTH in patients with ABD:**

The calcimimetics and the calcilytics.

The calcimimetic agent cinacalcet has a half-life of <24 h and initially reduces iPTH levels markedly, but this is followed by a strong iPTH rebound in plasma so that circadian swings of plasma iPTH increase.

Restoring the pulsatile PTH secretion pattern cont….

The calcilytic agents, which temporarily block the calcium sensing receptor at the parathyroid gland and thereby promote PTH secretion, may also help to stimulate bone turnover by increasing the pulsatile PTH secretion pattern.

- The oral calcilytic agent NPS 2143 has been applied to a model of bone loss and osteopenia (ovarectomized rats) and compared with the action of s.c. PTH. Increases of plasma PTH after the administration of NPS 2143 were prolonged (>4 h) in contrast to short increases with s.c. PTH.

Restoring the pulsatile PTH secretion pattern cont.…

- Indeed, both agents stimulated bone turnover.
- However, NPS 2143 resulted in a dramatic increase in both bone formation and resorption, with no net effect on bone mass. In contrast, PTH also increased both resorption and formation, but formation exceeded resorption, resulting in increased bone mass.

ABD: closing remarks

- **ABD** is not an innocent bystander in **CKD** .
- It is possibly the most prevalent bone lesion in advanced **CKD**, is associated with impaired calcium metabolism and linked to cardiovascular disease and mortality in **CKD** patients.
- **ABD** is, at least in part, often iatrogenic and it is this part in particular, which lends itself to prevention or therapeutic intervention.
- Reducing the calcium load is the best investigated preventive or therapeutic option in non-aluminium induced **ABD**.

Thank you

Prof. Dr.
Montasser Zeid
Faculty of Medicine
Alexandria University

MontasserZeid @yahoo.com